UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/788,410	03/01/2004	Robert L. Martuza	066683-0198	4953

22428 7590 04/13/2011
FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER	
SHEN, WU CHENG WINSTON	
ART UNIT	PAPER NUMBER
1632	

MAIL DATE	DELIVERY MODE
04/13/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/788,410
Filing Date: March 01, 2004
Appellant(s): MARTUZA ET AL.

Stephen A. Bent
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed on January 27, 2011 appealing from the Office action mailed May 26, 2011.

It is noted that the references listed in the IDS filed on 09/08/2010 and the IDS filed on 05/21/2010 have been considered. For the clarity of record, a copy of English translation of JP 8-127542, publication date 05/21/1996 (the reference G1 listed in the IDS filed on 05/21/2010) is included with the Examiner's Answer because the English translation of JP 8-127542 cannot be found in the record of instant application.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal. Nevertheless, as stated on page 22 of appeal brief filed by Applicant on 01/27/2011, Applicant indicates that an appeal is pending in Application No. 11/097,391.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

(I) U.S. patent 6,172,047 Roizman et al. Jan. 9, 2001

(II) Vile et al., Targeting of cytokine gene expression to malignant melanoma cells using tissue specific promoter sequences. Ann Oncol. 5 Suppl 4:59-65, 1994

(III) Chang et al., A gene delivery/recall system for neurons which utilizes ribonucleotide reductase-negative herpes simplex viruses, Virology, 185(1):437-40, 1991

(IV) WO 92/14821, PCT/US92/01375 Sep. 03, 1992

(V) US patent 5,639,656, Wright, Jr. June 17, 1997

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

(I). Claims 16, 28, and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Roizman et al.** (U.S. patent No. 6,172,047, issued Jan. 9, 2001; priority date 03/31/1992) in view of **Vile et al.** (Vile et al., Targeting of cytokine gene expression to malignant melanoma cells using tissue specific promoter sequences. Ann Oncol. 5 Suppl 4:59-65, 1994).

Claim 16 filed on 03/12/2010 reads as follows: A herpes simplex virus with a genome that comprises (i) an expressible non-herpes simplex virus nucleotide sequence encoding a cytokine capable of eliciting an immune response against a tumor cell, and (ii) an alteration in the γ34.5 gene such that no functional γ34.5 gene product is made, wherein the neurovirulence of said herpes simplex virus is attenuated.

Claim 28 is directed to the herpes simplex virus of claim 16, wherein an essential viral gene product of said virus is under the control of a tumor cell-specific promoter rather than its own viral promoter.

Claim 29 is directed to a composition comprising the herpes simplex virus of claim 16 and a pharmaceutically acceptable vehicle for said virus.

Claim interpretations: The limitation "capable of eliciting an immune response against a tumor cell" recited in amended claim 16 are the properties of recited cytokine. "Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

Roizman et al. teaches the following: **(i)** Novel modified HSV vectors for gene therapy (See abstract, Roizman et al., 2001), which reads on the limitation "an expressible non-herpes simplex virus nucleotide sequence" recited in claim 16 of instant applicant application, **(ii)** The function of the gene γ34.5 in its ability to enable the virus to replicate, multiply and spread in the central nervous system (CNS) was demonstrated by a set of recombinant viruses and by testing their abilities to cause fatal encephalitis in the mouse brain. The mutant viruses lacking the gene therefore lost their ability to multiply and spread in the CNS and eyes and therefore are non-pathogenic. See Chou et al., Science, 250: 1212-1266, 1990 (See lines 35-42, col. 4, Roizman et al., 2001), **(iii)** The use of the HSV-1 virus with a null mutation in the γ34.5 gene provides a method of therapeutic treatment of tumorogenic diseases both in the CNS and in all other parts of the body. The *"γ34.5 minus"* virus can induce apoptosis and thereby cause the death of the host cell, but **this virus cannot replicate and spread**. Therefore, given the ability to target tumors within the CNS, the γ34.5 minus virus has proven a powerful therapeutic agent for hitherto virtually untreatable forms of CNS cancer (See **bridging paragraph, col. 5-6**, Roizman et al., 2001). Roizman et al. further teaches that the γ34.5 gene placed under a suitable target specific

promoter in the context of treating a tumor cell [which reads on the limitation of claim 28 of instant application] would be expressed, thus inducing an anti-apoptotic effect in the neuron without the potential for stress induced neurovirulence (See lines 44-46, 56-60 col. 6, Roizman et al., 2001), and **(iv)** The embodiment of the present invention describes a method which involves combining ICP34.5 (i.e. γ34.5) or a biological functional equivalent thereof with a pharmaceutically acceptable carrier in order to form a pharmaceutical composition, which reads on claim 29 of instant application.

Roizman et al., do not teach a herpes simplex virus with a genome that expresses an exogenous cytokine gene recited in claim 16.

Vile et al. teaches that **(i)** transduction of tumor cells in vitro with cDNA encoding various cytokines and/or immune accessory molecules has been shown to diminish or eliminate tumorigenicity when such cells are returned in vivo to syngeneic animals (See first sentence of Introduction, page S59, Vile et al., 1994), **(ii)** constitutively producing cytokines such as IL-2, IL-4, and GM-CSF could be use as "cancer vaccine" by activation of immune system (See conclusions, right column, second paragraph, Vile et al., 1994), and **(iii)** use of the 5' flanking region of the murine tyrosinase gene directs expression of three different cytokine genes murine interleukin 2 (IL-2), IL-4 and macrophage colony-stimulating factor (M-CSF) specifically to murine melanoma cells (See abstract, Vile et al. Ann Oncol. 5 Suppl 4:59-65, 1994).

Therefore, it would have been prima facie obvious to one having ordinary skill in the art at the time of the invention to combine the teachings of Roizman et al. (2001) regarding the characteristics of a mutant herpes simplex virus comprising a disrupted γ34.5 gene of herpes simplex virus, which is non-pathogenic and has lost ability to multiply and spread in the CNS

and in all other parts of the body, with the teachings of Vile et al. (1994) regarding exogenous expression of a cytokine gene results in diminishment or elimination of tumorigenicity of tumor cells via elicitation of immune response, to arrive at the claimed HSV with disrupted both γ34.5 that exhibits no neurovirulence, and expressing a cytokine gene that elicit an immune response against a tumor cell, as recited in claims 16, 28, and 29 of instant application.

One having ordinary skill in the art would have been motivated to combine the teachings of Roizman et al. with the teachings of Vile et al. (1994) because (i) the γ34.5 gene mutation would result in a non-pathogenic vector, as taught by Roizman et al., 2001 (See last paragraph, column 5), and (ii) the exogenous expression of a cytokine gene would result in diminishing or eliminating tumorigenicity of tumor cells, as taught by Vile et al.

There would have been a reasonable expectation of success given (1) the demonstration that the "γ34.5 minus" virus can induce apoptosis and thereby cause the death of the host cell, but this virus cannot replicate and spread, by the teachings of Roizman et al., 2001, (2) the demonstration of exogenous expression of IL-2 coding sequences driven by a tissue specific promoter via direct injection in the murine melanoma cells completely abrogated their tumorigenicity in syngeneic mice, by the teachings of Vile et al., 1994.

Thus, the claimed invention as a whole was clearly prima facie obvious.

(II). Claims 18-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Roizman et al.** (U.S. patent No. 6,172,047, issued Jan. 9, 2001; priority date 03/31/1992) in view of **Vile et al.** (Vile et al., Targeting of cytokine gene expression to malignant melanoma cells using tissue specific promoter sequences. Ann Oncol. 5 Suppl 4:59-65, 1994) as applied to claims 16, 28, and

29 above, and further in view of **Chang et al.** (Chang et al., A gene delivery/recall system for neurons which utilizes ribonucleotide reductase-negative herpes simplex viruses, Virology, 185(1):437-40, 1991).

Claim 16 filed on 03/12/2010 reads as follows: A herpes simplex virus with a genome that comprises (i) an expressible non-herpes simplex virus nucleotide sequence encoding a cytokine capable of eliciting an immune response against a tumor cell, and (ii) an alteration in the γ34.5 gene such that no functional γ34.5 gene product is made, wherein the neurovirulence of said herpes simplex virus is attenuated.

Claim 18 is directed to the herpes simplex virus of claim 16, further comprising at least one further gene alteration.

Claim 19 is directed to the herpes simplex virus of claim 18, wherein said at least one further gene alteration is in the ribonucleotide reductase gene, such that no functional ribonucleotide reductase is made.

Claim 20 is directed to the herpes simplex virus of claim 19, wherein said herpes simplex virus is G207 expressing the cytokine.

Claim interpretations: The limitation "capable of eliciting an immune response against a tumor cell" recited in amended claim 16 are the properties of recited cytokine. It is noted that in the art G207, as recited in claim 20 of instant application, is the name of an HSV that contains deletions of both copies of the gamma34.5 gene as well as a LacZ insertion in the ICP6 gene, which is the large subunit (ICP6) of ribonucleotide reductase (RR).

The teachings of Roizman et al. and Vile et al. have been discussed in the preceding rejection of claims 16, 28, and 29 under 35 U.S.C. 103(a) as being unpatentable over Roizman et al. 2001 in view of Vile et al., 1994.

However, the combined teachings of Roizman et al. and Vile et al., do not teach a herpes simplex virus with a genome that comprises alteration in the ribonucleotide reductase (RR) gene (recited in claim 19 of instant application).

At the time of filing of instant application, a herpes simplex virus with a genome that is altered in the ribonucleotide reductase gene was known in the art. For instance, Chang et al. teaches that herpes simplex virus type-1 (HSV-1) is able to infect both non-neuronal and neuronal cells (See introduction, Chang et al., 1991). Chang et al. also teaches that ribonucleotide reductase (RR)-negative herpes simplex virus type-1 (HSV-1) is a useful vector for gene delivery into neuronal cells. Chang et al. used hrR3, a genetically engineered HSV-1 mutant which has an in-frame insertion of the bacterial LacZ gene into the HSV gene that encodes the large subunit (ICP6) of ribonucleotide reductase (RR), resulting in the ICP6::lacZ chimeric gene. Chang et al reported that the infection was performed in the presence of acyclovir; hrR3 appeared to become "latent". Chang et al. further teaches that the introduction of a foreign gene (e.g. a cytokine gene taught by Vile et al.) into neuronal cells by a RR-negative herpes simplex virus, and the subsequent induction of gene expression by another non-complementing virus, may constitute a prototype gene delivery/recall system for neurons (See abstract, Chang et al., 1991). Chang et al further teaches that ribonucleotide reductase (RR)-negative herpes simplex virus type-1 (HSV-1) grows in actively dividing cells, but the growth is severely impaired in growth arrested, non-dividing cells (See bridging paragraph, pages 437-438, Chang et al., 1991).

Therefore, it would have been prima facie obvious to one having ordinary skill in the art at the time of the invention to combine (i) the characteristics of a mutant herpes simplex virus

comprising an nucleotide sequence encoding a cytokine, a disrupted γ34.5 herpes simplex, which is non-pathogenic and has lost the ability to multiply and spread in the CNS and in all other parts of the body, as taught by combined teachings of Roizman et al. 2001 and Vile et al., 1994, with (ii) the characteristics of a RR-negative herpes simplex virus that can grow in actively dividing cells, but the growth is severely impaired in growth arrested, non-dividing cells, as taught by Chang et al. 1991.

It would have been obvious at the time of filing to combine the teachings of Roizman et al. 2001, and Vile et al., 1994, with the teachings of Chang et al. 1991, to arrive at the claimed herpes simplex viruses as recited in claims 18-20 of instant application.

One having ordinary skill in the art would have been motivated to combine the teachings of Roizman et al. 2001, Vile et al., 1994, with the teachings of Chang et al. 1991 because the disrupted γ34.5 gene renders the HSV vector non-pathogenic and the disrupted ribonucleotide reductase gene render the HSV vector specific targeting to fast dividing tumor cells without harming healthy cells, for the treatment of CNS or non-CNS cancers. Combination of the mutations would result in a non-pathogenic vector, as taught by Roizman et al., 2001 (See last paragraph, column 5), that targets specifically fast dividing tumor cells, as taught by Chang et al., 1991, which indicates the disruption of ICP6, either by LacZ insertion in the ICP6:LacZ strain or by deletion in the ICP6Δ strain, results in severe growth impairment in non-dividing cells (See first paragraph, left column, page 438).

There would have been a reasonable expectation of success given (1) the demonstration that the "γ34.5 minus" virus can induce apoptosis and thereby cause the death of the host cell, but this virus cannot replicate and spread, by the teachings of Roizman et al., 2001, (2) the

demonstration of exogenous expression of IL-2 coding sequences driven by a tissue specific promoter via direct injection in the murine melanoma cells completely abrogated their tumorigenicity in syngeneic mice, by the teachings of Vile et al., 1994, and (3) the demonstration that ribonucleotide reductase (RR)-negative herpes simplex virus type-1 (HSV-1) vector for introduction of a foreign gene can grow in actively dividing cells, but the growth is severely impaired in growth arrested, non-dividing cells, by the teachings of Chang et al., 1991.

Thus, the claimed invention as a whole was clearly prima facie obvious.

(III). Claim 30-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Roizman et al.** (U.S. patent No. 6,172,047, issued Jan. 9, 2001; priority date 03/31/1992) in view of **Vile et al.** (Vile RG and Hart IR, Targeting of cytokine gene expression to malignant melanoma cells using tissue specific promoter sequences. Ann Oncol. 5 Suppl 4:59-65, 1994) as applied to claim 16, 28, and 29 above, and further in view of **McKay et al.** (WO 92/14821, publication date 09/03/1992, PCT/US92/01375, priority date 02/22/1991), and **Wright, Jr.** (US 5,639,656, issued Jun. 17, 1997, filed 03/31/1994).

Claim 16 filed on 03/12/2010 reads as follows: A herpes simplex virus with a genome that comprises (i) an expressible non-herpes simplex virus nucleotide sequence encoding a cytokine capable of eliciting an immune response against a tumor cell, and (ii) an alteration in the γ34.5 gene such that no functional γ34.5 gene product is made, wherein the neurovirulence of said herpes simplex virus is attenuated.

Claim 30 is directed to the herpes simplex virus of claim 28, wherein said tumor cell-specific promoter is nestin promoter.

Claim 31 is directed to the herpes simplex virus of claim 28, wherein said tumor cell-specific promoter is basic fibroblast growth factor promoter.

Claim 32 is directed to the herpes simplex virus of claim 28, wherein said tumor cell-specific promoter is epidermal growth factor promoter.

Claim interpretations: The limitation "capable of eliciting an immune response against a tumor cell" recited in amended claim 16 are the properties of recited cytokine.

The teachings of Roizman et al. and Vile et al. have been discussed in the preceding rejection of claims 16, 28, and 29 under 35 U.S.C. 103(a) as being unpatentable over Roizman et al. 2001 in view of Vile et al., 1994.

However, the combined teachings of Roizman et al. and Vile et al., do not teach a herpes simplex virus with a genome that expresses a exogenous cytokine gene, wherein an essential viral gene product of said virus is under the control of a tumor cell-specific promoter rather than its own promoter, wherein said promoter being nestin promoter, basic fibroblast growth factor (bFGF) promoter, or epidermal growth factor (EGF) promoter, as recited in claims 30-32 of instant application.

At the time of filing of instant application, it was known in the art that the expression of certain growth factor genes including bFGF, EGF, nestin genes can serve as markers for detection of various cancers, indicating the promoters of these growth factors being tumor specific with respect to its regulation. For instance, McKay et al. teaches that nestin expression as an indicator of neuroepithelial brain tumors, indicating the nestin promoter being tumor specific with respect to its regulation (See title and abstract, WO 92/14821, publication date 09/03/1992). Wright, Jr. 1997 teaches the expression of bFGF, EGF can be used as biological markers of prostate cancer (CaP) or benign prostate hyperplasia (BPH) (See title and lines 30-36. column 2, Wright et al., 1997). Furthermore, as indicated before, Roizman et al. further

teaches that the γ34.5 gene placed under a suitable target specific promoter in the context of treating a tumor cell (which reads on claim 28 of instant application) would be expressed, thus inducing an anti-apoptotic effect in the neuron without the potential for stress induced neurovirulence (See lines 44-46, 56-60 col. 6, Roizman et al., 2001). Accordingly, it would have been prima facie obvious the nestin promoter, bFGF promoter, EGF promoter are tumor cell specific promoters, and thereby can be used for expressing an essential viral gene as recited in claims 30-32 of instant application by the combined teachings of Roizman et al., 2001, Vile et al., McKay et al., 1991, and Wright, 1997.

Therefore, it would have been prima facie obvious to one having ordinary skill in the art at the time of the invention to exogenously express a nucleotide sequences encoding a cytokine, whose transduction of tumor cells with cDNAs encoding various cytokines has been shown to diminish or eliminate tumorigenicity in syngeneic animals, in a γ34.5 defective HSV vector, as taught by the combined teachings of Roizman et al., 2001 and Vile et al., 1994, and to have an essential viral gene product under the control of a tumor cell-specific promoter of nestin or bFGF, or EGF, as taught by the teachings of Wright or McKay et al., in the said herpes simplex virus vector with disrupted both γ34.5 and expressing nucleotide sequences encoding a cytokine, to ensure that the said HSV vector exhibits no neurovirulence to non-cancer cells, by the combined teachings of Roizman et al. 2001 and Vile 1994.

It would have been obvious at the time of filing to combine (i) the teachings of Roizman et al. 2001, and Vile et al., 1994, regarding a HSV vector for cancer treatment with the expression of a nucleotide sequences encoding a cytokine from a HSV vector, wherein as essential viral gene product placed under a suitable target specific promoter, with (ii) the

teachings by Wright or McKay et al., regarding gene product being under the control of the tumor specific promoters of nestin or bFGF, or EGF to arrive at the claimed herpes simplex viruses as recited in claims 30-32 of instant application.

One having ordinary skill in the art would have been motivated to utilize the HSV vector that exhibits characteristics favorable gene transfer, expresses nucleotide sequence encoding a cytokine, and infects specifically to tumor cells, by combined teachings of Roizman 2001, Vile et al., 1994, to introduce the expression of a nucleotide sequences encoding a cytokine for gene therapy, and said HSV vector comprises an essential gene product under the control of the tumor specific promoters of nestin or bFGF, or EGF, by the teaching of Wright or McKay et al., becasue the HSV vector being non-pathogenic and specifically infect tumor cells without harming healthy cells, and the exogenous nucleotide sequence encoding cytokine is expressed only in the tumor cells, as an essential viral gene product is expressed in a tumor specific manner.

There would have been a reasonable expectation of success given (1) the demonstration that the "γ34.5 minus" virus can induce apoptosis and thereby cause the death of the host cell, but this virus cannot replicate and spread, by the teachings of Roizman et al., 2001, (2) the demonstration of exogenous expression of IL-2 coding sequences driven by a tissue specific promoter via direct injection in the murine melanoma cells completely abrogated their tumorigenicity in syngeneic mice, by the teachings of Vile et al., 1994, (3) the demonstration of nextin expression in a brain tumor specific manner by the teachings of McKay et al, and the expression of bFGF and EGF in a prostate cancer specific manner by the teachings of Wright.

Thus, the claimed invention as a whole was clearly prima facie obvious.

(10) Response to Argument

Appellant's arguments have been addressed in the order in which they have been presented in the appellant's appeal brief.

The appellant states the following arguments in pages 9-12 of appeal brief.

(II) Rejection over Roizman and Vile

(A) The skilled artisan would have been disincentivized from combining the vector-design elements of oncolytic activity and cytokine expression

In the prior art, the endeavors of HSV vector administration and cytokine expression belonged to different therapeutic domains, oncolytic viral therapy and cytokine gene therapy, respectively. See response filed on December 18, 2008, at pages 5 and 6. When the present application was filed, one skilled in the art would have been directed away from affecting the design of an HSV vector, a modality of virus-mediated oncolytic therapy, with an element of classical gene therapy, the heterologous expression of a cytokine.

The appellant state the examiner committed a number of errors, any one of which justifies reversal of the appealed rejections.

First, the examiner improperly invoked "inherency" to substantiate the rejection. Appellants have never denied that cytokines have the property of eliciting an immune response. Still, the examiner has invoked the notion "inherency" here in isolation, i.e., with reference to the cytokine alone rather than to the context of the claimed invention. Consequently, the examiner's analysis downplayed the key issue of whether the skilled artisan would have introduced cytokine expression into the design of an oncolytic HSV vector, notwithstanding the a priori unpredictability of the field at the time and the potentially confounding (anti-infective) impact of such cytokine expression.

Second, the recited feature of eliciting an immune response should not be mislabeled as an "intended use," denying it patentable weight. Rather, the claim recitation in question sets forth

a property or feature of appellants' invention, namely, the capability of eliciting an immune response against tumor cells. The examiner cites no valid basis for refusing patentable weight to the recitation, regardless of the type of claim.

Third, the posited combination of the cited art cannot be justified, as the examiner has, on the pseudo-mathematical basis of "1+1=2" additivity. The examiner asserts, because cancer treatment is a goal both of the gene therapy represented by Vile ("1") and of the oncoloytic therapy represented by Roizman ("1"), that it thus would have been obvious to combine features drawn from the respective therapies, apparently for some additive effect on anti-cancer efficacy ("1+1=2"). See final Office Action, the paragraph bridging pages 8 and 9.

(B) The examiner erroneously downplayed a priori unpredictability in the relevant field and instead imposed an a posterori "additivity" to justify combining otherwise disparate teachings on oncolytic therapy and oncytokine expression, respectively

Appellant asserted that, at the time of appellants' invention, the skilled artisan in this new field would have received insubstantial guidance, if any, from the art on balancing the largely uncharacterized variables of vector design to achieve both oncolytic and cytokine efficacy. Accordingly, there would have been no principled way of predicting a priori the outcome, in terms of cancer treatment, of combining the presently recited features, drawn from oncolytic therapy and gene therapy (cytokine expression). By way of illustration in this regard, appellants enumerated the following scenarios to show what the skilled artisan would have had to consider, in principle, without basis in any previous experience or demonstrated principle:

(a) if the expression of cytokine elicits an immune response that eliminates the HSV-infected host cells before HSV accomplishes the oncolytic effects, the net effect of the combined therapy is nothing more than the cytokine efficacy;

(b) if the replication of HSV kills the host cells before a sufficient amount of cytokine is expressed, the only benefit achieved is the oncolytic viral therapy; and

(c) if the replication of HSV parallels the immune response caused by the cytokine expression, the HSV is able to spread in tumor cells while the cytokine eliciting an anti-tumor immune response.

In response, it is worth emphasizing that the claimed subject matters are product claims. Claim 16 reads as follows: A herpes simplex virus with a genome that comprises (i) an expressible non-herpes simplex virus nucleotide sequence encoding a cytokine capable of eliciting an immune response against a tumor cell, and (ii) an alteration in the γ34.5 gene such that no functional γ34.5 gene product is made, wherein the neurovirulence of said herpes simplex virus is attenuated. As stated in Claim interpretation: The limitation "capable of eliciting an immune response against a tumor cell" recited in amended claim 16 are the properties of recited cytokine. "Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

The Examiner had clearly acknowledges that the properties of a given cytokine are not identical the properties of another cytokine. In this regard, **Varghese et al.** teaches enhanced therapeutic efficacy of IL-12, but not GM-CSF, expressing oncolytic herpes simplex virus for transgenic mouse derived prostate cancers using the same series of HSV vector reported by Liu et al. (2005) (See title and abstract, Varghese et al., Enhanced therapeutic efficacy of IL-12, but not GM-CSF, expressing oncolytic herpes simplex virus for transgenic mouse derived prostate cancers, Cancer Gene Ther. 13(3):253-65, 2006) (See pages 17-18 of the Final office action mailed on 05/26/2010). Therefore, Appellant's previously asserted unexpected results of IL-12 taught by Liu et al., based on the unexpected nature, cannot be extrapolated to any other cytokine (See pages 17-18 of the Final office action mailed on 05/26/2010).

Nevertheless, directed relevant to the claimed products recited in claim 16 with regard to "capable of eliciting an immune response against a tumor cell" recited in amended claim 16 in cytokine-mediated cancer gene therapy, **Vile et al.** (i.e. the second reference cited in the first 103(a) rejection) teaches that **(i)** transduction of tumor cells in vitro with cDNA encoding various cytokines and/or immune accessory molecules has been shown to diminish or eliminate tumorigenicity when such cells are returned in vivo to syngeneic animals (See first sentence of Introduction, page S59, Vile et al., 1994), **(ii)** constitutively producing cytokines such as IL-2, IL-4, and GM-CSF could be use as "cancer vaccine" by activation of immune system (See

conclusions, right column, second paragraph, Vile et al., 1994), and **(iii)** use of the 5' flanking region of the murine tyrosinase gene directs expression of three different cytokine genes murine interleukin 2 (IL-2), IL-4 and macrophage colony-stimulating factor (M-CSF) specifically to murine melanoma cells (See abstract, Vile et al. Ann Oncol. 5 Suppl 4:59-65, 1994). Furthermore, the teachings by Vile et al. (1994) are consistent with the teachings of the status of art at the time of filing. For instance, **JP 8-127542** (publication date 05/21/1996, G1 reference cited in the IDS filed on 05/21/2010) teaches the same subject matters regarding gene therapy agent for cancer vaccine introduced into tumor cell by viral vectors and tumor cell effector cytokine genes (See summary of English translation of JP 8-127542). As a related issue, it is worth noting that the statements by Vile et al. "Clearly, the in situ genetic modification of neoplastic cells provides an attractive and, by contrast, simpler approach to novel molecular therapy. However, such in situ gene therapy would require a specificity of gene delivery that is impossible using currently available viral vectors or physical transfer techniques" (See left column, page S59, Vile et al.) are referred to "genetic modification of neoplastic cells" in situ at genomic DNA level (i.e. alteration of endogenous cytokine gene expression), not as Appellant argues that it is impossible to express a cytokine from a HSV vector (i.e. exogenous cytokine gene expression) for cytokine-mediated vaccination against cancer cells.

Furthermore, oncolytic viral therapy and cytokine gene therapy are two closely related research fields as exemplified by JP 8-127542 discussed in the preceding paragraph, rather than two unrelated fields as Appellant argues. In this regard, bearing the goal of targeting specifically to cancer cells in mind, Chang et al. [See the rejection of claims 18-20 under 35 U.S.C. 103(a)] teaches that ribonucleotide reductase (RR)-negative herpes simplex virus type-1 (HSV-1) grows in actively dividing cells (e.g. cancer cells), but the growth is severely impaired in growth arrested, non-dividing cells (See bridging paragraph, pages 437-438, Chang et al., 1991). Chang et al. further teaches that the introduction of a foreign gene (which encompasses a cytokine gene taught by Vile et al.) into neuronal cells by a RR-negative herpes simplex virus, and the subsequent induction of gene expression by another non-complementing virus, may constitute a prototype gene delivery/recall system for neurons (See abstract, Chang et al., 1991) (See page 8 of Final office action mailed on 05/26/2010).

With regard to the arguments pertaining to multiple possible scenarios, including scenarios (a) to (c) discussed by Appellant. The Examiner had acknowledged that even as of current status of art, the outcome of a given cancer gene therapy in general remains unpredictable and needs to be evaluated on a case-by-case basis. However, it is worth emphasizing, again, the claims of instant application is directed to a product, not a method of using said product in cancer gene therapy that results a statistically significant reduction in tumor growth, as Appellant argues. In this regard, it is noetd that the breadth of claimed products encompass a HSV with null mutation of both γ34.5 and any cytokine gene expressed from any promoter and inserted in any position in the HSV genome. The claimed HSV structure as a whole was clearly prima facie obvious based on the combined teachings of Roizman et al. (U.S. patent No. 6,172,047, issued Jan. 9, 2001) in view of Vile et al. (Ann Oncol. 5 Suppl 4:59-65, 1994). The efficacy of a given species encompassed by the breadth of claimed HSV in cancer gene therapy depends on the the properties of a given cytokine inserted in a given position of claimed HSV, which the Examiner agree with Appellant that the breadth of the claimed HSV in treating a given cancer of interest remains unpredictable, as Appellant argues that several possible scenarios may occur. Nevertheless, **Vile et al.** specifically teaches that **(i)** transduction of tumor cells in vitro with cDNA encoding various cytokines and/or immune accessory molecules has been shown to diminish or eliminate tumorigenicity when such cells are returned in vivo to syngeneic animals (See first sentence of Introduction, page S59, Vile et al., 1994), **(ii)** constitutively producing cytokines such as IL-2, IL-4, and GM-CSF could be use as "cancer vaccine" by activation of immune system (See conclusions, right column, second paragraph, Vile et al., 1994), and **(iii)** use of the 5' flanking region of the murine tyrosinase gene directs expression of three different cytokine genes murine interleukin 2 (IL-2), IL-4 and macrophage colony-stimulating factor (M-CSF) specifically to murine melanoma cells (See abstract, Vile et al. Ann Oncol. 5 Suppl 4:59-65, 1994). Accordingly, a skilled person in the art would be motivated to make the claimed HSV based on the combined references and to test how effective the claimed HSV may be in a given cancer gene therapy of interest (See pages 11-12 of the Final office action mailed on 05/26/2010).

The appellant states the following arguments in pages 13-17 of appeal brief.

(C) The examiner improperly dismissed the declaration evidence proffered in rebuttal of the examiner's obviousness rationale

Appellants submitted the Rabkin declaration in part to substantiate the fact that one of ordinary skill would have been discouraged from combining the cited references as the examiner has posited, given the known, counteracting effects of cytokine expression on the HSV oncolytic activity (see above). Appellant asserts that Examiner Shen discounted the declaration evidence, however, (i) by substituting his own judgment, without basis, for an expert's opinion and (ii) by asserting that the declaration evidence is not commensurate in scope with the claimed invention.

(i) The examiner's impression should not outweigh the declarant's averment

Despite the declaration evidence, the examiner found no impediment in the art to combining disparate elements drawn from gene therapy and oncolytic therapy because "[t]here is no contradiction for the goal.., of cancer treatment.., to ultimately kill cancer cells without harming normal cells" (final Office Action at page 9, lines 3-5). Yet, the examiner has said nothing about the declarant's attestations concerning an art-recognized contradiction in mechanism. See Rabkin declaration at paragraph 4. Again, the examiner's analysis improperly downplayed or ignored the impact of a contradiction perceived in the art, prior to appellants' invention, between the host cell-protective effect of cytokine expression and the serial infection/lysis of host cells, which is essential to the efficacy of an oncolytic HSV vector as claimed.

(ii) The declaration evidence is commensurate in scope with the claimed invention because the skilled artisan would have recognized a reasonable correlation between the claimed HSV vector and the HSV vectors encompassed by the declaration

Appellant states that, on two occasions the examiner asserted that appellants' rebuttal evidence is not commensurate in scope with the claims. In one instance, the examiner contends that Exhibits A, C, F and H accompanying Rabkin's declaration and the publication by Ghiasi (submitted on July 20, 2009) are not commensurate in scope with the claims because the HSV vectors illustrated by Exhibits A, C, F and H do not have the same null mutations of y34.5 and ribonucleotide reductase. See final action, the paragraph bridging pages 12 and 13. In terms of Ghiasi, the examiner further asserted that “the claimed HSV [is] already non-pathogenic/virulent

due to the presence of γ34.5 mutation" (id).

Appellant states that, although the claimed HSV vector is attenuated for its virulence, it still is required to be replication-competent in dividing cells, e.g., cancer cells. Therefore, as evidenced by Exhibits A, C, F and H, as well as by Ghiasi, showing that cytokine expression blocks infection and replication of HSV, the skilled artisan reasonably would have made a correlation with the claimed HSV vector, based on the common feature of "replication-competence," and hence would have anticipated that cytokine expression likewise would have blocked the replication of the claimed HSV vector in dividing cells.

Appellant states that, on the other occasion, the examiner contended that evidence proffered on the NV1042 vector illustrated in Liu's publication (submitted on July 20, 2009) is not commensurate in scope with the claimed invention. See, in the final action, the paragraph bridging pages 16 and 17. There is no factual basis in the present record, however, for the examiner to label the γ34.5 mutation as "the most critical element" (see below) and to eschew, in this context, the common feature shared by the HSV vectors. In the response filed on March 12, 2010, appellants urged that their rebuttal evidence is commensurate with the claimed invention because the HSV mutants exemplified by the cited publications are in the same category of HSV vectors delineated by the claims, i.e., the category of replication-competent, oncolytic HSV vectors. Thus, the skilled artisan would have understood that the HSV vector of Liu is reasonably correlated with the claimed HSV vector because both are attenuated, replication-competent, oncolytic HSV vectors.

In response, the following statements have been documented on pages 12-14 of the Final office action mailed on 05/26/2010.

It is worth noting that none of declaratory evidence provided in Exhibits A, C, F, and H that accompanies the Rabkin Declaration is commensurate in scope with the claimed HSV products --- i.e. a HSV with null mutation of both γ34.5 and ribonucleotide reductase and any cytokine gene inserted in the HSV genome. Similarly, the provided post-filing reference Ghiasi et al. (2002) teaches the use of HSV to express IL-2 under LAT promoter (i.e. promoter for late gene expression) in the context of evaluation of replication and virulence the HSV that does not

comprise the γ34.5 mutation, which renders the HSV non-pathogenic and cannot replicate and spread in CNS, and ribonucleotide reductase mutation, which render HSV replicates in dividing cancer cells but not in non-dividing cells. Post filing art Ghiasi et al. (2002) showed that (i) IL-2 appears to protect against ocular HSV infection, as HSV-IL-2 proved to be less virulent than either the wild-type virus or its marker-rescued virus (the survival of mice co-infected with the parental virus and HSV-IL-2 was higher than that of mice infected with the parental virus alone, and depletion of IL-2 resulted in increased virulence of HSV-IL-2) and (ii) the ability of IL-2 to protect against ocular HSV-1 infection appears to be related to the activity of both the CD4+ and CD8+ T-cell populations, as depletion of either type of T cell resulted in a higher mortality rate upon HSV-IL-2 infection (See left column, page 9070, Ghiasi et al.). However, the data presented by Ghiasi et al. (2002) do not provide any relevant information regarding claimed HSV expressing a cytokine from a HSV that comprises both γ34.5 mutation and ribonucleotide reductase mutation because the claimed HSV are already non-pathogenic/virulent due to the presence of γ34.5 mutation, even in the absence of the effect of IL-2 expression from LAT promoter in the HSV taught by Ghiasi et al. Therefore, there is no asserted disincentive for any skilled artisan to combine the teachings of Roizman et al. with the teachings of Vile et al. (1994), especially in light of the teachings by Vile et al. that transduction of tumor cells in vitro with cDNA encoding various cytokines and/or immune accessory molecules has been shown to diminish or eliminate tumorigenicity when such cells are returned in vivo to syngeneic animals (See first sentence of Introduction, page S59, Vile et al., 1994). Furthermore, Vile et al teaches that expression of IL-2 in the murine melanoma cells completely abrogated their tumorgenicity in syngeneic mice (See right column, summary, page S59) and loss of tumorgenicity correlates with continued IL-2 expression (see right column, page 62), the skilled artisan would have reasonable expected that the expression of IL-2 from a viral vector, such as claimed HSV, would enhance the anti-tumor effects of the virus. Appellant is also reminded that the fact that Appellant may have recognized another characteristic and/or advantage of claimed product (e.g. reducing tumor growth) which would flow naturally from following the suggestion of the prior art (i.e. Roizman et al. and Vile et al. in this case) cannot be the basis for patentability when the

differences would otherwise be obvious. See Ex parte Obiaya, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

With regard to Appellant's arguments that Examiner's position that cytokine gene cloned in the claimed HSV would only be expressed **after** the HSV has infected cells is "not well-conceived", the Examiner notes that a virus, by definition, can only become a living entity inside a host cell. In other words, a virus cannot become alive and actively express a gene in the absence of host cellular machinery. Therefore, contrary to Appellant's assertion that the cytokine gene cloned in the claimed HSV would only be expressed **after** the HSV has infected *cells is Examiner's **"impression"**, the Examiner's position in this regard, is based on the* fundamental knowledge and well-accepted definition of what a virus is. This fundamental and well-accepted knowledge of a virus is fully supported by the status of art, for instance, **Bolovan et al.** teaches ICP34.5 mutants of herpes simplex virus type 1 strain 17syn+ are attenuated for neurovirulence in mice and for replication in confluent primary mouse embryo cell cultures, and that viral stocks were generated by routine passage in rabbit skin cell cultures (See title and Material and Methods, Bolovan et al., ICP34.5 mutants of herpes simplex virus type 1 strain 17syn+ are attenuated for neurovirulence in mice and for replication in confluent primary mouse embryo cell cultures, J. Virol. 68(1):48-55, 1994; This reference has been cited in the IDS filed by Applicant on 10/06/2004).

Furthermore, Appellant appeared to agree with the Examiner's position pertaining to cytokine gene cloned in the claimed HSV would only be expressed **after** the HSV has infected cells, otherwise it would have been meaningless for Appellant to argue and propose three possible scenarios (a) to (c) regarding how the timing of cytokine gene expression may affect oncolytic activity of claimed HSV. In this regard, it should be emphasized that Dr. Rabkin's declaration and the Exhibits A, C, F, and H are directed to **endogenous** cytokine gene expression to protect host cell from HSV infection (i.e. pre-existing cytokine **before virulent** HSV infection) and diminish replication of HSV in the host cells (See pages 10-13 of the Non-Final office action mailed on 08/18/2008), which is in contrast to the claimed products of instant application regarding **exogenous** cytokine expression from **non-pathogenic** HSV **after** HSV has infected host cells.

Additionally, the following statements have been documented on pages 16-18 of the Final office action mailed on 05/26/2010.

With regard to the teachings by Liu et al., Cancer Res. 65:1532-40 (2005) (present Exhibit 2), demonstrating that an HSV vector expressing IL-12 is significantly better at inhibiting tumor growth than the "NV1042" HSV vector alone, which Applicant asserted as unexpected (synergistic) result, the Examiner notes that "NV1042" HSV vector is not commensurate in scope with the claimed HSV products because the "NV1042" HSV vector taught by Liu et al. comprise deletion in ICP47 gene. Moreover, nowhere in the teachings by Liu et al. indicates any greater than additive or unexpected effect when IL-12 is expressed from the "NV1042" HSV vector as compared to the effect of IL-12 and the effect of NV1042" HSV individually. Furthermore, disclosure of a post-filing art being consistent with Applicant's intended use of claimed products does not constitute unexpected results. It is also noted that any evidence of unexpected results must be commensurate in scope with the claimed invention, and that a greater, or greater than additive, effect is not necessarily sufficient to overcome a prima facie case of obviousness because such an effect can either be expected or unexpected MPEP 716.02 (a) and (d). "Expected beneficial results are evidence of obviousness of a claimed invention, just as unexpected results are evidence of unobviousness thereof." In re Gershon, 372 F.2d 535, 538, 152 USPQ 602, 604 (CCPA 1967); Ex parte Blanc, 13 USPQ2d 1383 (Bd. Pat. App. & Inter. 1989). Even if the results of Liu et al. were to be considered as unexpected as Applicant asserted, it is further noted that the teachings of IL-12 is not commensurate in scope with the claimed HSV products --- i.e. any cytokine expressed from a HSV with null mutation of both γ34.5 and ribonucleotide reductase. In this regard, the asserted unexpected results of IL-12 taught by Liu et al., based on the unexpected nature, cannot be extrapolated to any other cytokine. Consistent with this rationale, **Varghese et al.** teaches enhanced therapeutic efficacy of IL-12, but not GM-CSF, expressing oncolytic herpes simplex virus for transgenic mouse derived prostate cancers using the same series of HSV vector reported by Liu et al. (2005) (See title and abstract, Varghese et al., Enhanced therapeutic efficacy of IL-12, but not GM-CSF, expressing oncolytic herpes simplex virus for transgenic mouse derived prostate cancers, Cancer Gene Ther. 13(3):253-65, 2006). Therefore, taken together as discussed in this paragraph, the asserted unexpected results based on the post-filing art by Liu et al. (2005) cannot overcome the

prima facie obvious case based on the combined teachings of Roizman et al. in view of Vile et al.

The appellant states the following arguments in page 17 of appeal brief.

(III) Rejection over Roizman, Vile and Chang

Claims 18-20 do not stand or fall with claim 16 because they benefit from additional grounds of patentability due to the examiner's misinterpretation of Chang.

Appellant states that In the final office action, the examiner further cited Chang for the alleged teaching of "the introduction of a foreign gene (e.g. a cytokine gene taught by Vile et al.)." See page 8, lines 11- 15. In fact, Change does not even hint at introduction of a cytokine gene. Rather, Chang describes knocking out ICP6 gene by a deletion of part of the ICP6 gene or by an in-frame insertion of a lacZ gene into the ICP6 gene. See the abstract and page 438, left column. Expression of a lacZ gene is quite different from expression of a cytokine gene. In the former instance the gene serves as an expression marker, with no known contradicting effects to the host cells. In the latter instance, by contrast, expression of a cytokine gene would have been deemed a confounding factor in the context of oncolytic therapy (see above). Accordingly, Chang adds no weight to the examiner's rejection rationale.

In response, Examiner's Responses to Appellant's arguments are the same as discussed in the preceding rejection of claims 16, 28, and 29 as being unpatentable over Roizman et al. in view of Vile et al. Furthermore, as stated on page 28-29 of the Final office action mailed on 05/26/2010, regarding the motivation to combine the cited reference, it is worth adding that, bearing the goal of targeting specifically to cancer cells taught by Roizman et al. and Vile et al., Chang et al. teaches that ribonucleotide reductase (RR)-negative herpes simplex virus type-1 (HSV-1) grows in actively dividing cells (e.g. cancer cells), but the growth is severely impaired in growth arrested, non-dividing cells (See bridging paragraph, pages 437-438, Chang et al., 1991). Chang et al. further teaches that the introduction of a foreign gene (which encompasses a cytokine gene taught by Vile et al.) into neuronal cells by a RR-negative herpes simplex virus,

and the subsequent induction of gene expression by another non-complementing virus, may constitute a prototype gene delivery/recall system for neurons (See abstract, Chang et al., 1991).

The Examiner notes that the teachings by Chang et al. regarding "The introduction of a foreign gene into neuronal cells by a RR-negative herpes simplex virus, and the subsequent induction of gene expression by another non-complementing virus, may constitute a prototype gene delivery/recall system for neurons" is not limited to the gene delivery of a lacZ reporter gene as a foreign gene, as exemplified by Chang et al. A skilled artisan in gene therapy mediated by HSV vector would certainly understand that lacZ reporter gene serve as a test for evaluation of delivery efficiency by HSV vector due to its ease in detection and lacZ is certainly not a cytokine. The process of cloning a foreign gene of interest into a HSV vector requires the same molecular cloning techniques and considerations (e.g. restriction enzyme digestion, ligation reaction etc). It is worth noting again, the breadth of claimed products encompass a HSV with null mutation of both γ34.5 and any cytokine gene expressed from any promoter and inserted in any position in the HSV genome. The claimed HSV structure as a whole was clearly prima facie obvious based on the combined teachings of Roizman et al. (U.S. patent No. 6,172,047, issued Jan. 9, 2001) in view of Vile et al. (Ann Oncol. 5 Suppl 4:59-65, 1994).

(IV). Rejection over Roizman over Vile, McKav and Wright

The teachings of Roizman and Vile are discussed above. McKay and Wright are cited for the alleged teaching of tumor-specific promoters. Yet, such teaching does not cure the above-discussed deficiencies of the primary reference and the secondary references, respectively.

In response, the Examiner's Responses to Appellant's Arguments are the same as discussed in the preceding rejection of claims 16, 28, and 29 as being unpatentable over Roizman et al. in view of Vile et al.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Wu-Cheng Winston Shen/
Primary Examiner, Art Unit 1632

Conferees:

/Peter Paras, Jr./
Supervisory Patent Examiner, Art Unit 1632

/Joseph T. Woitach/
Supervisory Patent Examiner, Art Unit 1633